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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/727,311	11/29/2000	William D. Huse	P-IX 4526	3119

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EXAMINER	
LAMBERTSON, DAVID A	
ART UNIT	**PAPER NUMBER**
1636	13

DATE MAILED: 08/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/727,311	HUSE, WILLIAM D.	
	Examiner	Art Unit	
	David A. Lambertson	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 May 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 88-91* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 88-91* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☒ Interview Summary (PTO-413) Paper No(s). *13* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Receipt is acknowledged of a reply, filed May 19, 2003 as Paper No. 12, to the previous Office Action. Amendments were not made to the claims.

Claims 1 and 88-91 are pending and under consideration in the instant application. Any rejection of record in the previous Office Action, Paper No. 7, mailed February 23, 2002, that is not addressed in this action has been withdrawn.

Because this Office Action only maintains rejections set forth in the previous Office Action, this Office Action is made FINAL.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 88-91 are rejected under 35 U.S.C. 102(e) as being anticipated by Ladner *et al.* (US Patent No. 5,223,409; see entire document; henceforth Ladner). **This rejection is maintained for reasons set forth in the previous Office Action.**

Response to Arguments Concerning Claim Rejections - 35 USC § 102

Applicant's arguments filed May 19, 2003 have been fully considered but they are not persuasive. The main point of applicant's argument focuses on the signal sequence that is employed to direct the surface expression of the gene VIII fusion protein that is claimed. The crux of applicant's argument is that Ladner is not enabled as of the priority date for it's parent application 07/487,063, filed March 2, 1990, thus Ladner should not be granted the priority date of March 2, 1990. As a result, Ladner would not have a sufficient filing date to serve a prior art under 35 USC § 102(e), thus the rejection should be withdrawn. Applicant's specific arguments regarding the non-enablement of Ladner are as follows:

1. Ladner does not provide reasonable guidance to practice the invention without undue experimentation because Ladner merely discusses the pros and cons of substituting heterologous signal sequences, and does not resolve the concerns because it simply drafts prophetic examples. The earliest application (07/240,160, filing date September 2, 1988) only provides a hypothetical example (see applicant's Exhibit 1), the problems of which are not solved by the discussion of additional possible alternatives in the '063 application (see applicant's Exhibit 2).

2. Ladner simply suggests the use of other signal sequences in the event that the putative gene VIII signal sequence does not direct the fusion protein for surface expression (see applicant's Exhibit 3). This is an invitation to experiment, and cannot be construed as guidance.

3. Ladner provides contradictory teachings, first saying that the gene VIII signal sequence works (see applicant's Exhibit 3), then saying it does not work (see applicant's Exhibits 6 and 7), and finally providing evidence that it did work, at least partially (see applicant's Exhibit 8). Applicant then suggests that these contradictory teachings raise doubts as to whether or not the other working examples cited in Ladner also worked.

4. Applicant questions why Ladner did not remove the hypothetical description regarding the use of the gene VIII signal sequence in the '063 application, when it was removed in the patent that issued.

5. Applicant suggests that the teachings of Ladner using other signal sequences besides the gene VIII signal sequence lack sufficient guidance. This is because of the contradictory statements regarding the gene VIII signal sequence, despite teachings that other sequences did work (see applicant's Exhibit 9, particularly regarding the *phoA* signal sequence).

6. According to applicant, a subsequent scientific paper published by the Ladner group also contradicts the results presented in the '063 application. This paper (see applicant's Exhibit 10) (a) indicates again that the gene VIII signal sequence did not work; (b) does not indicate the presence of the MB42 constructs' processed protein which is indicated as present in the application (indicated as a "+"); (c) is inconclusive as it regards the "+/-" data concerning the gene VIII signal sequence because of a molecular weight discrepancy; and (d) questions the accuracy of the quantitation of the "+++" results when comparing the results seen in the paper versus the '063 patent.

Based on these arguments, applicant suggests that the '063 application was not enabled at the time of filing. Therefore, applicant requests that the Ladner reference be withdrawn as prior art under 102(e) art.

Applicant's arguments filed May 19, 2003 have been fully considered but they are not persuasive. Before addressing each individual argument presented by applicant, the examiner would like to make a few general comments as it regards applicant's argument. First, applicant is respectfully reminded that, in order for a specification to be enabling, it does not require that each and every embodiment within the scope of the claims be enabled. Thus, there may be non-enabled species within the scope of the invention, yet the application may still be enabled. This is determined by the examiner for each application on a case-by-case basis. Second, the examiner has thoroughly reviewed the parent application (the '063 application) of the Ladner patent that is being questioned, in an attempt to uncover any evidence that the examiner for the '063 application felt the application was not enabled. However, no evidence of an enablement rejection was present in the '063 application at the time of this Office Action. Finally, the unpredictability of an invention requires both that there be no forethought to potential problems associated with the enabling of the invention, and that the unpredictability be associated with a part of the invention that is vital to the practice of the invention (e.g., the Nature of the Invention). In other words, in order for a particular invention to be non-enabled, the unpredictability must be associated with a vital part of the invention, and must not have been predicted to be a problem with potential or working solutions.

1. The '063 application does indeed provide a solution to the hypothetical problems regarding the use of a heterologous signal sequence to target the surface expression of a gene VIII fusion

protein. In fact, the Ladner application provides a specific working example using a *phoA* signal sequence that directs the surface expression of a gene VIII fusion protein (see for example page 259 and Table 108 of the '063 application as presented in applicant's Exhibits 8 and 9). This working example addresses the use of heterologous signal sequences to direct the surface expression of a gene VIII fusion protein, thereby addressing the hypothetical problems regarding the use of a heterologous signal sequence. Furthermore, there is no evidence that the previous examiner found this example non-enabled for the full scope of the invention, as indicated by the issue of the 5,223,409 patent made of record and the apparent absence of an enablement rejection in the '063 parent application.

2. Ladner does more than simply suggest the use of different heterologous signal sequences. Ladner exemplifies a particular signal sequence, *phoA*, as it regards its ability to direct the surface expression of a gene VIII fusion protein (again see for example page 259 and Table 108 of the '063 application as presented in applicant's Exhibits 8 and 9). This is not merely an invitation to further experimentation, as the experimentation was clearly done and found operational. Furthermore, Ladner clearly indicates that (a) the signal sequence is not the important feature of the invention, going so far as to suggest that multiple different sequences can be substituted for the signal sequence and (b) that the primary feature of the invention is the retention of the mature coat protein (see applicant's Exhibit 3, lines 7-9 and 10-15). Ladner discusses that the purpose of the signal sequence is simply the targeting of the surface expression of the gene VIII fusion protein, and the skilled artisan would clearly recognize that substituting any known signal sequence would not incur undue trial and error experimentation. Applicant is respectfully reminded that this method is not directed to finding new signal sequences, but

instead to the surface expression of a fusion protein using known signal sequences. Thus, the '063 specification serves as sufficient guidance to the skilled artisan, indicating to them that other signal sequences may be substituted in the fusion protein so long as the mature gene VIII coat protein is maintained. This is further supported by the fact that a working example is presented using a heterologous signal sequence (*phoA*), which effectively directs the surface expression of a gene VIII fusion protein (again see for example page 259 and Table 108 of the '063 application as presented in applicant's Exhibits 8 and 9).

3. The teachings of Ladner are not necessarily interpreted as contradictory because Ladner clearly indicates that the signal sequence of the gene VIII fusion protein can be substituted (and in fact may require substitution) with a different signal sequence. Ladner indicates that the signal sequence is not the primary feature of the invention, and that it's only requirement is to properly target the fusion protein for surface expression. The fact that a substitute signal sequence (*phoA*, as shown in applicant's Exhibit 8) was able to provide this function cannot be questioned due to the failure of a different signal sequence (e.g., the gene VIII signal sequence), especially when that failure was predicted, provided for with a rational alternative (a different sequence; e.g., *phoA*), and overcome using the alternative. The fact that Ladner predicted the potential drawbacks to the gene VIII sequence begs the question as to how the invention can be unpredictable if Ladner recognized the potential problem and then provided a working remedy by using the *phoA* signal sequence. In essence, applicant is apparently trying to argue that if one embodiment is not enabled, then one must question the enablement of all embodiments. However, this is not an acceptable argument as a patent is allowed to have non-enabled embodiments.

4. The inclusion of a hypothetical example that does not work again raises the issue of arguing the non-enablement of one embodiment equates to the non-enablement of all embodiments. As discussed above, this is not an acceptable argument when there are clearly enabled embodiments (e.g., the use of the *phoA* signal sequence).

5. The suggestion of Ladner to substitute different heterologous signal sequences for the putative gene VIII signal sequence is found to provide sufficient guidance to the skilled artisan to enable the invention for the following reasons. First, Ladner clearly indicates that the signal sequence is not the most important feature of the invention (see applicant's Exhibit 3 as indicated above), and goes so far as to suggest using different sequences for the simple purpose of directing the surface expression of the gene VIII fusion. Second, Ladner actually successfully demonstrates the ability to substitute the signal sequence with the *phoA* signal sequence, supporting the assertion that the signal sequence can be substituted. Finally, this is not determined to be an invitation to experimentation because a successful example of the experimentation is presented, and because the experimentation involves a feature that Ladner clearly indicates is not the primary feature of the invention.

6. The teachings of the Markland publication (applicant's Exhibit 10) are not found to be contradictory to the teachings of the '063 application. In this paper, it is clearly demonstrated that the *phoA* sequence results in the proper processing of the gene VIII fusion protein, which equates to its surface expression (the signal sequence is processed upon entry into the surface membrane- see Figure 2, lanes 12 and 13 and the corresponding text of the publication). Applicant's primary argument here is that the quantitation presented in the '063 patent (as "+++") is not commensurate with the processed protein in the Markland paper (see specifically

lanes 12 and 13). Applicant tries to establish this argument by comparing the expression level of the processed protein in lanes 12 and 13 to the unprocessed protein in lanes 9 and 10. This appears to be a groundless argument because applicant is arguing the expression levels of two different constructs where there is no direct correlation between the constructs. Irrespective of this observation, any perceived error in the quantitation between the '063 application and the Markland publication (or lanes therein) does not change the fact that the *phoA* sequence resulted in the surface expression of the gene VIII fusion protein in both the '063 application and the Markland reference. Therefore, the Markland paper appears to affirm the results indicated in the '063 application because the *phoA* signal sequence resulted in the surface expression of a gene VIII fusion protein.

In conclusion, applicant's argument that the Ladner reference was not enabled as of the priority date (the filing date of the 07/487,063 application) is not convincing. First, applicant is arguing about the deficiencies in an element of the invention which Ladner both discusses as a relatively minor part of the invention and recognizes as a potential source of trouble but with obvious and suggested remedies. The primary points made by applicant are that (a) the use of a gene VIII signal sequence did not properly target the gene VIII fusion protein for surface expression, (b) that contradictory results concerning the effectiveness of the gene VIII signal sequence raises doubt as to the efficacy of other signal sequences used to target the gene VIII fusion for surface expression, (c) that applicant did not provide sufficient guidance with regard to the use of different signal sequences resulting in an invitation for further experimentation, and (d) that a post-filing publication contradicts the teachings of the priority application. Concerning points (a) and (b), Ladner is allowed to have non-enabled embodiments, and these non-enabled

embodiments cannot question embodiments that have been demonstrated to work, such as the use of the *phoA* signal sequence to target the surface expression of a gene VIII fusion protein. Concerning (c), Ladner provided sufficient guidance for the use of different signal sequences because they predicted a potential need to use such sequences, and then demonstrated the effectiveness of using a different signal sequence (*phoA*). Concerning (d), the post-filing publication actually indicates that the *phoA* sequence did indeed suffice to target the surface expression of a gene VIII fusion; applications assertion that the efficiency of this targeting shown in the paper is not commensurate with that shown in the '063 application is groundless because the fact of the matter is that the targeting occurred, as evidenced by the processing of the signal sequence form the gene VIII fusion protein. Applicant has not provided sufficient evidence to question the enablement of the '063 application for these reasons. The bottom line is that the *phoA* signal sequence was clearly demonstrated in the '063 application to target the surface expression of a gene VIII fusion protein, thereby enabling the invention. This is then supported by the results in Figure 2 of the Markland reference. Furthermore, the examiner sees no reason to contradict the previous examiner, who apparently had not raised enablement issues in the '063 application. As a result, Ladner is maintained as prior art under 35 USC § 102(e).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 1 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 29 of U.S. Patent No. 6,258,530 (henceforth the '530 patent). **This rejection is maintained for reasons set forth in the previous Office Action.**

Response to Arguments Concerning Double Patenting Rejections

Applicant's arguments filed May 19, 2003 have been fully considered but they are not persuasive. Applicant's arguments are as follows:

1. Claims 1 and 29 of the '530 patent do not render claim 1 of the instant application obvious because claim 1 of the '530 patent is directed to particular and distinct modes of expression of a peptide.

Applicant's arguments are not found convincing for the following reasons:

1. First, claim 1 of the '530 patent is a species claim that anticipates the genus claim 1 of the instant application. Claim 1 of the instant application is drawn to a plurality of cells containing a diverse population of expressible oligonucleotides linked to expression elements, wherein the oligonucleotides have a desirable codon bias and are produced by random combinations of precursor sequences. Similarly, claim 1 of the '530 patent is also drawn to a plurality of cells containing a diverse population of expressible oligonucleotides linked to expression elements

wherein the oligonucleotides have a desirable codon bias and are produced by random combinations of precursor sequences, although there are additional limitations such as the presence of a suppressible stop codon. However, the more specific claim 1 of the '530 patent falls within the scope of the broader claim 1 of the instant specification, thereby anticipating the instant claim 1. Thus the instant claim 1 is obvious in view of claim 1 of the '530 patent, although the scopes are not identical. Thus, the fact that claim 1 of the '530 patent is drawn to a particular and distinct mode of expression does not obviate the rejection of instant claim 1 under the doctrine of obviousness-type double patenting. Second, although applicant does not readily address this part of the rejection, the combination of the limitations of claims 1 and 29 of the '530 patent also results in claim 1 of the instant application. To make the record clear, claim 29 of the '530 patent is a much broader claim than claim 1 of the '530 application, and encompasses the full scope of the claim. Therefore, it would have been obvious to combine/subtract any of the limitations set forth in claim 1 of the '530 patent to arrive at a claimed invention that is within the broad scope of claim 29, and motivation to arrive at the invention comes the desire to obtain as complete a coverage for the invention as possible. A particular combination of claim 1 in view of claim 29 would result in the same embodiment that is claimed in claim 1 of the instant application. Thus the combination of claims 1 and 29 of the '530 patent also makes instant claim 1 obvious. For both of the reasons set forth above, the rejection under the judicially created doctrine of obviousness-type double patenting is maintained.

Allowable Subject Matter

No claims are allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David A. Lambertson whose telephone number is (703) 308-8365. The examiner can normally be reached on 6:30am to 4pm, Mon.-Fri., first Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on (703) 305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

David A. Lambertson
August 7, 2003

DAVID GUZO
PRIMARY EXAMINER